MALARIA IN PREGNANCY

Plenary Presentation

Malaria Control for Pregnant Women.
Umberto D'Alessandro

Summary Report on Breakout Session

Programme

Summary Report

PLENARY PRESENTATION

Malaria Control for Pregnant Women

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The prevalence of malaria is increased during pregnancy compared to the non-pregnant state (Gilles et al, 1969; Brabin et al, 1988; Kortman, 1972; Brabin et al, 1990a). Susceptibility to infection and the severity of clinical manifestations are determined by the level of pre-pregnancy immunity which, in turn, depends largely on the intensity and stability of malaria transmission (Mutabingwa, 1994). In highly endemic areas, such as most of sub-Saharan Africa, the effects of malaria on mother and foetus are less severe than in areas with low or unstable transmission, but malaria still has important consequences for pregnancy, especially in primigravidae. It has been repeatedly reported that primigravidae usually have a higher prevalence of malaria infection (peripheral or placental) as compared to multigravidae (Keuter et al, 1990; Mvondo et al, 1992; Bulmer et al, 1993; Meuris et al, 1993; Mutabwinga et al, 1993), and that the difference between infected and non-infected women in mean Hb levels (Kortman, 1972; McGregor, 1984; Brabin et al, 1990) as well as in mean birth weight (Jelliffe, 1968; Kortman, 1972; McGregor et al, 1983) are more marked in primigravidae than in multigravidae. However, multigravidae are also vulnerable to malaria as it has been shown by recent data from Senegal. The incidence of malaria attacks during pregnancy as compared to control time periods (before or after pregnancy) in the same women was significantly and substantially increased also for multigravidae up to their fifth pregnancy (Diagne et al, 1997). This makes the proposition of limiting malaria chemoprophylaxis to primigravidae not only impractical from an operational point of view but also difficult to justify in view of the above data. There are still a few questions to be answered in terms of the consequences of malaria for pregnant women and their offsprings. For example, the role of malaria as a contributing factor to abortion, perinatal mortality and prematurity is unknown (Menendez, 1995), although for the latter a significant reduction after the implementation of a national programme on insecticide-treated nets (ITN) has been reported (D'Alessandro et al, 1996). The effect of malaria during pregnancy on the infant's susceptibility to infection and on mortality is also unknown, although it is likely that increasing the mean birth weight as result of malaria prevention would increase the chances of survival.

Since 1964, about 300 papers reporting, directly or indirectly, on malaria control measures during pregnancy have been published. However, this is still a controversial subject. A recent Cochrane review on malaria prevention in pregnant women identified only 14 trials meeting the authors' strict inclusion criteria (Gulmezoglu & Garner, 1999). The trials used different antimalarial drugs (chloroquine, pyrimethamine, mefloquine dapsone-pyrimethamine) and different chemoprophylaxis regimens (daily, weekly, fortnightly and monthly). A significant decrease of antenatal parasitaemia was found in most of the studies (Fleming et al, 1986; Greenwood et al, 1989; Mutabingwa et al, 1993a; Nosten et al, 1994; Nyirjesy et al, 1993). A small effect on packed cell volume was detected, although it appeared to be confined mainly to primigravidae (Hamilton et al, 1972; Greenwood et al, 1989; Nosten et al, 1994). There was a trend towards a higher mean birth weight, mainly in primigravidae (Morley et al, 1964; Hamilton et al, 1972; Greenwood et al, 1989; Cot et al, 1992; Nosten et al, 1994; Nyirjesy et al, 1993). None of the trials, because of their relatively small size, had sufficient power to detect a possible effect on perinatal and neonatal mortality and surrogate and intermediate outcomes of infant death, which include placental parasitaemia,

are of doubtful significance (Gulmezoglu & Garner, 1999). The conclusions of the Cochrane review is that given the existing evidence, effectiveness of prophylaxis on relevant outcomes is not strong: it seems to protect from illness in the mother and increase birth weight in primigravidae. Study sizes mitigate against any conclusions in terms of obstetric morbidity or fetal/infant mortality (Gulmezoglu & Garner, 1999). However, several trials were not included in the above review because they did not meet the necessary requirements or have been published after the review. It is worthwhile considering that the results of the largest chemoprophilaxis trial ever done during pregnancy was excluded because of suspected bias in the allocation of the 4 regimens under evaluation. The study, the Mangochi Malaria Research Project carried out in Malawi, evaluated three different chloroquine (CQ) regimens against mefloquine (MQ) (Steketee et al, 1996). In each of the 4 centres participating to the trial where pregnant women were enrolled, one of the three CQ regimens was compared to a MQ regimen by alternation (days of the week). The method reported should have led to a 1:1 ratio of women given mefloquine:chloroquine. However, there were four times as many women in the chloroquine group (3077 vs 1032) and this is the reason why the results were not considered for the Cochrane review (Gulmezoglu & Garner, 1999). Nevertheless, the results can still be of relevance when considering the impact of chemprophylaxis during pregnancy. At the time of the study chloroquine resistance in Malawi was already high. The risk of persistent or breakthrough malaria infection was much higher among women on CQ as compared to those on MQ (OR: 30.9 and OR: 11.1 respectively) (Steketee et al, 1996). The risk of peripheral or placental parasitaemia was also higher in women on CQ (OR: 8.7 and 7.4 respectively). The percentage of low birth weight babies was lower in the MQ than in the CQ group (12.5% vs 15.5%). These results indicate that an effective antimalarial drug can prevent malaria infection during pregnancy and can have a beneficial effect on its outcome.

An alternative approach is the administration of intermittent presumptive treatment, which may achieve equal efficacy to continuous chemoprophylaxis. This has been investigated in Malawi where a two-dose regimen of sulfadoxine-pyrimethamine (SP) (one dose in the second trimester followed by a second dose at the beginning of the third) were compared with one dose of SP or one treatment of CQ followed by weekly CQ. The results show a significant impact of the 2-dose SP regimen on peripheral and placental parasitaemia and a tendency towards a higher mean birth weight and a lower percentage of low birth weight babies (Schultz et al, 1994). A recent published trial carried out in Malawi found a significant difference in mean birth weight and percentage of LBW in women who had received two or three doses of SP during pregnancy compared to those who had received only one dose (Verhoeff et al, 1998). However, 1. the study was not a randomised controlled trial and assigned different doses of SP according to the weeks of gestation at time of first antenatal clinic; 2. data were available only for 31% of the women recruited; 3. the number of SP doses did not have any effect on placenta or peripheral parasitaemia at delivery and on Hb concentration. Two additional trials carried out in Kenya compared intermittent treatment with SP with placebo or routine case management. One showed a significant decrease of severe anaemia in pregnant women on SP but not on the occurrence of LBW or on mean birth weight (Shulman et al, 1999). The other showed also an impact on mean birth weight and the percentage of LBW babies (Parise et al, 1998).

SP intermittent treatment seems effective in preventing some of the consequences of malaria infection in pregnant women. However, some questions still remain. Before the 16th week of pregnancy SP is not recommended because of concerns on possible

teratogenicity (Phillips-Howard & Wood, 1996). Furthermore, SP intermittent treatment has been compared either with a placebo or with weekly CQ prophylaxis, which was likely to be ineffective because of the high level of resistance already present. None of the above studies compared effective weekly malaria chemoprophylaxis with effective intermittent treatment. This should caution us in implementing SP intermittent treatment everywhere, even in places where CQ remains still the first line treatment. There have been several reports on the interaction between HIV infection and malaria during pregnancy (Verhoef et al, 1999). Two doses of SP during pregnancy seem insufficient to confer adequate protection to HIV+ women and the number of doses to be given to this particular group of women is still unknown. The lower efficacy of SP when given together with folic acid raises the question on whether these 2 drugs should be given together to pregnant women.

Insecticide-treated nets (ITN), which are effective at reducing malaria in children and adults (D'Alessandro et al, 1995), offer a possible alternative approach to the control of malaria in pregnancy. However, the evidence on whether ITN or just untreated nets during pregnancy are of practical benefit is insufficient (Gulmezoglu & Garner, 1999). The first trial was carried out in 3 refugee camps on the Thai-Burmese border (Dolan et al, 1993). A significant reduction in the incidence of *vivax* and *falciparum* malaria was observed in only one camp but a significant reduction of anaemia was recorded in all 3 camps. The size of the net significantly influenced the degree of protective efficacy; malaria and anaemia occurred more frequently in the group using untreated single-size bednets distributed by the investigators than in those using 'family untreated bednets' which were large enough for 2 or 3 persons. No beneficial effect of ITN on birth weight was shown. Another trial carried out in Kenya and involving about 500 primigravidae was unable to show any significant impact of ITN on different factors (severe anaemia, peripheral and placental parasitaemia, birth weight)(Shulman et al, 1998). However, the ITN national programme in The Gambia had some impact limited to the malaria transmission season on primigravidae (D'Alessandro, 1996). Mean birth weight, prevalence of parasitaemia at 32 weeks of gestation, percentage of premature babies were significantly different in primigravidae living in villages where nets had been treated with insecticide.

Whatever the strategy used to control malaria during pregnancy and although this should cover all pregnant women, primigravidae remain the most vulnerable group to be specifically targeted. Unfortunately, this is the group that is more difficult to reach. In The Gambia, for example, the mean age of 651 primigravidae was 17 years, most of them were farmers and illiterate. Although most of them attended an antenatal clinic at least once (mean number of attendance: 4), received some iron and folic acid supplementation, only a small minority received some chemoprophylaxis (D'Alessandro, 1996). The iron and folic acid supplementation did not have any effect on mean PCV levels, the percentage of anaemia (Hb≤8) at 32 weeks of gestation was 18%.

Despite available data on different interventions retain some uncertainties, it is possible to reduce the burden of malaria among pregnant women, just by using current knowledge. However, one of the major problems for programme managers and implementers remains how to translate the available information in feasible and sustainable programmes. How to improve the delivery and coverage of such interventions, particularly for primigravidae? There is the need of promoting collaboration between scientists and policy makers/health managers in order to answer these questions and so doing, contributing to the decrease of the burden of disease among pregnant women. A recently developed initiative, **PRE**gnancy

Malaria and **A**naemia (PREMA), aiming at answering the above needs will try to facilitate the communication between control and research communities. This is an essential step for optimizing the implementation of excisting research findings.

The proposed activities of PREMA are:

1. To create a compendium of current national malaria control policies targeted at pregnant women in African countries in order to know what is done and how this differs between countries;
2. To review available data on the efficacy, effectiveness, acceptability and operational feasibility of different strategies for malaria control during pregnancy and to produce guidelines for national programmes;
3. To identify gaps in knowledge and to develop appropriate research protocols when needed;
4. To create consensus documents and position papers on issues relating to malaria in pregnancy for wide dissemination through peer reviewed journals and to Governments, NGOs and donor agencies;
5. To sensitise and inform, by means of a newsletter and other publications, policy makers and national governments of research findings on malaria in pregnancy and of their implications for malaria control programmes in endemic areas;

Strategies aiming at improving the health of pregnant women in malaria endemic countries will be successful only if a dialogue between scientists and implementers is promoted and the current scientific knowledge applied in the best possible way.

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BREAKOUT SESSION: MALARIA IN PREGNANCY

Programme

Malaria in Pregnancy

Chairs: Dr. Theonest Mutabingwa and Dr. Steve Allen

Rapporteurs: Dr. Clara Menendez, Dr Umberto d'Alessandro

1. Basic science question, where are we now? - Clara Menendez (10 mins).
2. Pregnancy associated enhanced susceptibility to malaria persists three months after delivery - Nefissatou Diagne (5 mins).
3. *Plasmodium falciparum* and pregnancy in Cameroon: malaria prevalence of T cells responses - R. Magnekou (5 mins).
4. Data needs for preparing strategies for malaria control in pregnancy – Caroline Shulman (10 mins).
5. Assessment of malaria in pregnancy and antimalarial drug resistance, Koro, northern Mali – Mary Mungai (5 mins).
6. Prophylaxis in pregnancy - Pascal Magnussen (10 mins).
7. Managing malaria in pregnancy - Alan Macheso (10 mins).
8. A randomised controlled trial on malaria control in pregnancy in Ejisu-Juoben District, Ghana - Edmund Browne (5 mins).
9. New tools for measuring the impact of malaria control in pregnancy - Steve Allen (10 mins).
10. The role of bednets for malaria control in pregnancy. - Jo Lines (5 mins).
11. Malaria and HIV. - Bernard Nahlen (10 mins).
12. Recommendations from a recent WHO Expert meeting. A. Rietveld, Alastair Robb (5 mins).

General discussion.

Setting a Research Agenda relevant to control programmes. - Clara Menendez (Rapporteur).

Establishing the Pregnancy and Malaria Anaemia (PREMA) Network. - Umberto d'Alessandro (Rapporteur).

Summary Report: Malaria in Pregnancy

Clara Menedez reviewed what it is known in terms of biology and control of malaria during pregnancy. Several gaps in knowledge as well as controversies were identified. The mechanisms involved in the increased risk of malaria are still not completely understood. The effect of maternal parity and the impact of protection against malaria during pregnancy on the infants risk to malaria are unknown. The efficacy of intermittent antimalarial treatment at different immunity levels and the efficacy of impregnated bed nets compared with that of regular chemoprophylaxis or intermittent treatment needs also to be investigated. The interaction of sulfadoxine-pyrimethamine intermittent treatment with folic acid on the risk of malaria needs to be clarified as well as the potential use and efficacy in pregnancy of future malaria vaccines. Whether protection in high endemic areas should be restricted to specific groups of pregnant women at risk (primigravidae, severely anaemic, HIV seropositive) needs to be discussed.

N. Diagne presented data from Senegal showing that women of all parities had a higher incidence of clinical malaria during their pregnancy and early postpartum supporting the hypothesis that pregnancy-associated immuno-suppression, but not parasite sequestration in the placenta, is the leading mechanism involved in maternal malaria.

Rosette Magnekou confirmed that primigravidae are more susceptible than multigravidae to malaria infection and that the II trimester is the most vulnerable period when a down-regulation of T cell proliferative responses has been shown. Only 4 out of 24 countries included malaria in pregnancy as part of their plan of action (C. Shulman). A recent trial in Kenya showed a considerable impact of SP intermittent treatment on anaemia in primigravidae. The Kenya Malaria Control Unit was already in the process of changing policy to intermittent SP for women of all parities, based on evidence from Malawi, Kisumu and Kilifi. According to Shulman, although there are a number of questions requiring clarification, it is important not to wait until we have all of the answers before research findings are translated into policy. The new strategy should be implemented and at the same times safety and effectiveness should be monitored. The results of randomized, double-blind, placebo controlled intervention trial on chloroquine prophylaxis and iron/folic acid supplementation in Hoima District, Western Uganda were reported by Pascal Magnussen. Chloroquine prophylaxis and iron/folic acid supplementation both increased maternal Hb compared to case management and the effect increased with duration of prophylaxis. There was no difference in the increase in Hb between the two groups. Both chloroquine and iron/folic acid had additional advantages over case management alone on maternal Hb and fetal outcome. Alan Macheso reported on the Malawian experience of introducing SP intermittent treatment for pregnant women. In 1997 data from 2 sentinel sites indicate that maternal (5%), placental (6%) and cord (2%) parasitaemia are very low among pregnant women. However, there are problems with HIV + women.

A discussion after this first round of presentation followed. What is the impact (positive/negative) of chemoprophylaxis during pregnancy on infant mortality? Considering the present knowledge it is impossible to use a placebo to investigate such a question. It was proposed to use birth weight to predict the impact on infant mortality as it is known that this is linked to child survival. The evidence of the impact of SP intermittent treatment on birth weight is weak. Why this strategy should be promoted as policy? It was

pointed out that it was ethically impossible to look at anaemia and BW at the same time as anaemic women should be treated. However, the effect on maternal anaemia was large, at least in Kenya and this could justify the implementation of such policy. Anaemia in pregnant women is multifactorial and all of them should receive a supplement of iron and folic acid.

Edmund Browne presented the design of a trial comparing monthly chloroquine treatment with monthly SP treatment and with routine antenatal care in primigravidae and secundigravidae. The study is currently carried out in Ghana and aims at recruiting a total of 660 pregnant women. A new way of monitoring malaria transmission or malaria control measures in pregnancy was presented by Steve Allen. The normogram is based on the percentage low birthweight in primigravidae (Y axis) and the odds ratio for low birthweight in primigravidae compared to multigravidae (X axis). The normogram distinguished longitudinal changes in malaria exposure related to season and changes in antimalarial drug policy. As birth weight and parity are routinely recorded in many delivery centres across Africa, the normogram provides a simple, available and inexpensive tool for monitoring malaria transmission and exposure in pregnant women. Jo Lines discussed the role of insecticide-treated bednets (ITNs) on malaria control in pregnancy. It is still unclear whether ITNs give an additional benefit to pregnant women in terms of malaria control. They reduce exposure but is this enough to prevent the consequences of malaria infection? The interaction between malaria and HIV infection were discussed by Bernard Nahlen. HIV infection results in malaria-like symptoms and consequently in over use of antimalarial drugs. Aafje Rietveld presented the recommendations concerning malaria control in pregnancy from a recent WHO expert meeting.

The role of ITNs in malaria control during pregnancy is not clear. The question asked is whether the studies carried out so far had the power to detect such an effect. However, it is obvious that ITNs, even if they have an impact, it is not as big as that on mortality in children. Iron supplementation should be given to all pregnant women as there is no doubt that this is beneficial. The discussion pointed out also that future studies on pregnant women must avoid the use of placebo as the administration of chemoprophylaxis or intermittent treatment with SP has shown a clear benefit. Therefore, it would be unethical to have a control group only on placebo. The normogram on birth weight could be used to monitor the impact of the introduction of SP intermittent treatment.

Background

- malaria in pregnancy is a major cause of maternal mortality, maternal anaemia and low birthweight (LBW) in endemic areas
- the problem is often unrecognised because infected women are usually asymptomatic
- case management alone is not effective in preventing the adverse effects of malaria during pregnancy
- Preventive measures have clearly showed a positive impact on pregnant women and newborns

Research Priorities

Short-term

- appropriate tools are needed to monitor the effectiveness of current control programmes
- new methods are needed to improve the implementation and compliance with control strategies (eg. by the involvement of TBAs)
- monitoring the effectiveness of impregnated bednets in different endemic settings
- the cost-effectiveness of interventions in different settings needs to be assessed

Medium-term

- assessment of the combination of different preventive measures (eg. chemoprophylaxis/intermittent treatment and impregnated bednets)
- comparison of intermittent treatment (sulphadoxine-pyrimethamine) with regular, efficacious chemoprophylaxis
- more information regarding the efficacy of intermittent treatment with sulphadoxine-pyrimethamine in different endemic settings
- the negative interaction between HIV and malaria infection during pregnancy, in particular an increase in the vertical transmission of HIV and the increased susceptibility to malaria in HIV+ women
- the potential health implications of an increase risk to malaria in the post-partum period need to be explored
- the interaction between antifolate antimalarials and folic acid supplementation has to be assessed

Long-term

- new agents need to be developed to cope with the emergence of resistance to current drugs
- the importance of protection early in pregnancy needs further assessment
- more investigation of the mechanisms involved in the increased risk to malaria in pregnancy (eg. the role of binding to chondroitin sulphate)

Implications of current research results for the treatment and control of malaria

- case management alone is not effective in preventing the adverse effects of malaria during pregnancy
- there is clear evidence that protection should be offered at least to all primigravidae, women with severe anaemia including sickle cell disease and HIV+ women. In practice it may be more cost-effective to offer protection to all pregnant women. Questions remain regarding the choice of the drug, dosage, mode of delivery and implementation
- current strategies may be less effective in HIV+ women and this should be taken into account when planning and selecting interventions
- selection of the currently available preventive tools such as chemoprophylaxis, intermittent treatment and insecticide-impregnated bednets will need to be determined by local conditions
- it is likely that other interventions will need to be used in addition to impregnated bednets
- all women in endemic areas should receive haematinics during pregnancy
- interventions aimed at preventing malaria infection and its consequences during pregnancy need continuous monitoring. Key outcome measures are LBW

and maternal anaemia. The normogram for the excess-risk of LBW in primigravidae is a promising tool for the former.

Mechanisms for strengthening links between control and research communities

A recently developed initiative, PREgnancy Malaria and Anaemia (PREMA), is an attempt to facilitate communication between control and research communities. It is recognised that this is an essential step for optimising the implementation of existing research findings.

Research capacity needs

The effective development and implementation of control programmes will need inputs from several disciplines, including among others social anthropology, health economy. Training will also be needed to improve the ability of programme managers to monitor the impact of different intervention. There is also an urgent need for African scientists to be trained to undertake basic research.